Review

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Comparison of current global guidelines and consensus on the management of patients with cholangiocarcinoma: A 2026 update

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SUMMARY: Cholangiocarcinoma (CCA) is a highly aggressive, molecularly heterogeneous biliary tract malignancy and the second most common primary liver cancer, and it has an increasing global incidence and persistently poor prognosis. Recent updates of international guidelines, including those from the NCCN, ESMO, EASL, CSCO, BSG, and Japanese societies, along with rapid advances in precision oncology, have substantially changed the clinical management of CCA. This review systematically compares current global guidelines, highlighting both areas of consensus and regional differences in epidemiology, risk factors, screening strategies, diagnostic approaches, pathological and molecular classification, staging systems, surgical indications, systemic therapy, and multidisciplinary management. This review also summarizes recent advances in molecular diagnostics, including next-generation sequencing, liquid biopsy, circulating tumor DNA, extracellular vesicles, artificial intelligence-assisted imaging, radiomics, and emerging prognostic biomarkers. The evolving roles of immune checkpoint inhibitors, molecularly targeted therapies against FGFR2, IDH1, HER2, BRAF, NTRK, and MSI-H/dMMR, liver transplantation, locoregional treatment, and conversion (translational) therapy are also discussed. Finally, this review addresses current challenges, including drug resistance, limited access to molecular testing, regional disparities in healthcare resources, and the lack of universally accepted screening strategies. By integrating updated guideline recommendations with the latest clinical evidence, this review provides a comprehensive reference for evidence-based clinical decision-making and future translational research in CCA.

Keywords: cholangiocarcinoma, clinical guideline, precision oncology, molecular profiling, immunotherapy, targeted therapy

1. Introduction

Cholangiocarcinoma (CCA) constitutes a highly aggressive, molecularly diverse, and anatomically heterogeneous cluster of biliary tract malignancies originating from the epithelial cells of the biliary tree and is the second most common primary liver cancer after hepatocellular carcinoma (*1,2*). Based on anatomical location, CCA is classified into intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA), and distal cholangiocarcinoma (dCCA), with pCCA and dCCA collectively referred to as extrahepatic cholangiocarcinoma (eCCA) (*3,4*). The 2019 WHO classification further recognizes mixed hepatocellular-cholangiocarcinoma (cHCC-CCA) as a distinct subtype (*5*). Due to the lack of specific early symptoms and the heterogeneity of tumor biology, most patients with CCA are diagnosed in an advanced stage, resulting in a median overall survival (OS) of only 24 months after initial diagnosis (*2*).

In recent years, with advances in medical research and mounting clinical evidence, numerous clinical practice guidelines for CCA management have been updated globally, including those from the National Comprehensive Cancer Network (NCCN), the European Association for the Study of the Liver (EASL), the Chinese Society of Clinical Oncology (CSCO), the British Society of Gastroenterology (BSG), the European Society for Medical Oncology (ESMO), and the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) (*6*). These guidelines provide important references for clinical decision-making, but their recommendations differ due to differences in regional medical resources, epidemiological characteristics, and the incorporation of new evidence. The rapid development of targeted therapy and immunotherapy has significantly changed the treatment landscape of advanced CCA, requiring timely

integration into clinical practice guidelines and clinical decision-making (*7,8*).

This review systematically compares the core content of current CCA guidelines, analyzing their similarities and differences in epidemiology, risk factors, screening and diagnosis, staging, and treatment (Table 1). It then cites recent key studies to corroborate the latest progress in targeted therapy, immunotherapy, surgical techniques, and prognostic biomarkers in order to provide a comprehensive and up-to-date reference for the clinical management and scientific research of CCA.

2. Epidemiology and risk factors

2.1. Epidemiology

CCA is universally recognized as a rare malignancy, accounting for less than 1% of all human cancers; however, its incidence and mortality exhibit marked geographical heterogeneity. Its global age-standardized incidence ranges from 0.3 to 3.5 cases per 100,000 population in Europe, the US, and Australasia but is as high as 85 cases per 100,000 in liver fluke–endemic regions such as northeastern Thailand (*8,25*).

Notably, the incidence of iCCA has been rising steadily worldwide, and particularly in Western nations (*26*). From 2000-2019, the incidence of iCCA increased from 0.92 to 1.94 in the US (*27*). This trend is attributed to advances in diagnostic imaging, demographic shifts including migration, and the escalating burden of chronic liver disease (*7*). Conversely, the incidence of eCCA has remained the same or slightly declined in most regions (*28*). GBC, another subtype of biliary tract cancer, exhibits distinct epidemiological patterns: it is declining in most regions worldwide but remains elevated in South Korea and Japan (*10*).

2.2. Risk factors

Global guidelines uniformly identify chronic inflammation of the biliary epithelium as the core common risk factor for CCA, but there are differences in emphasis on subtype-specific risk factors (*25,29*).

The ESMO and EASL-ILCA guidelines list key risk factors for iCCA including cirrhosis, hepatitis B virus, hepatitis C virus, non-alcoholic fatty liver disease, diabetes, obesity, and hormonal contraceptives (*30*). According to the BSG guidelines, alcohol consumption and cigarette smoking are also associated with an increased risk of iCCA (*8,21*).

The main risk factors for pCCA are primary sclerosing cholangitis (PSC) in Western countries and hepatobiliary flukes or hepatolithiasis in Asian countries (*31*). The ESMO guidelines specify that the annual incidence of CCA in PSC patients is 0.6-1.5%, with a lifetime risk of up to 20%. The BSG guidelines add that choledochal cysts and choledocholithiasis are also high-risk factors for pCCA (*8,23*).

Gallstones are the strongest risk factor for GBC, followed by porcelain gallbladder, gallbladder polyps, PSC, chronic Salmonella typhi or Helicobacter bilis infection, congenital biliary tract malformations, and obesity. The ESMO guidelines emphasize that the incidence of GBC increases with age and that GBC is more common in women (*8*).

Notably, the bEASL-ILCA and BSG guidelines both mention that 60-70% of iCCA cases have no identifiable risk factors, highlighting the need for further exploration of unknown etiologies.

2.3. Hereditary cancer syndromes

A rapidly growing consensus across international guidelines in 2026 is the formal recognition of CCA within the expanding spectrum of hereditary cancer syndromes. CCA is part of the spectrum of hereditary cancer syndromes, including hereditary breast-ovarian

Table 1. Overview of recent major clinical practice guidelines and consensus statements on biliary tract cancers

Guidelines	Year	Country/Geographical area	Language	Tumor	*Ref.*
ENS guideline	2026	Europe	English	iCCA, pCCA, dCCA	(*9*)
NCCN guideline	2025	USA	English	iCCA, pCCA, dCCA and GBC	(*10*)
CSCO guideline	2025	China	Chinese	pCCA	(*11*)
Expert consensus	2025	China	English	pCCA	(*12*)
EASL guideline	2025	Europe	English	pCCA, dCCA	(*13*)
ESMO guideline update	2025	Europe	English	iCCA, pCCA, dCCA and GBC	(*14*)
SEOM-GEMCAD-TTD clinical guidelines	2025	Spain	English	iCCA, pCCA, dCCA and GBC	(*15*)
AFEF guideline	2024	French	English	iCCA, pCCA,	(*16*)
ILTS-ILCA guideline	2024	Europe	English	iCCA, HCC	(*17*)
IHPBA-APHPBA guideline	2024	USA	English	GBC	(*18*)
National guidelines	2024	Pakistan	English	hCCA	(*19*)
Canada guideline	2023	Canada	English	iCCA, pCCA, dCCA and GBC	(*20*)
EASL-ILCA	2023	Europe	English	iCCA	(*21*)
Italian guideline	2023	Italy	English	iCCA, pCCA, dCCA	(*22*)
BSG guideline	2023	UK	English	iCCA, pCCA, dCCA	(*23*)
ESMO guideline	2023	Europe	English	iCCA, pCCA, dCCA and GBC	(*8*)
JSHBPS guideline	2019	Japan	English	iCCA, pCCA, dCCA	(*24*)

cancer syndromes associated with BRCA1 and BRCA2 germline mutations, as well as germline mutations in ATM, CHEK2, and PALB2, and Lynch syndrome linked to mismatch repair deficiency (*32*). Studies have identified germline mutations in 2 to 16% of patients with CCA, including variants in APC, ATM, BAP1, BRCA1, BRCA2, FANCA, PALB2, PMS2, MUTYH, RAD51D, MLH1, and MLH2 (*33-35*). In patients with pCCA/dCCA, germline variants including BRCA1, BRCA2, MLH1, MSH6, MUTYH, ATM, CHEK2, FANCA, and APC have been documented (*34-36*). The BSG guidelines strongly advocate for taking a comprehensive family history to exclude familial cancer syndromes, specifically recommending that patients presenting with an unusual familial pattern of cancer or exceptionally early-onset disease be promptly referred to clinical geneticists (*23*).

3. Screening and diagnosis

3.1. Screening strategies

Due to the lack of universal screening standards, guidelines recommend targeted screening for high-risk populations based on regional risk factors. For PSC patients, the ESMO and EASL-ILCA guidelines recommend annual non-invasive imaging surveillance (ultrasound, MRI/MRCP) combined with CA 19-9 detection (*21,37*). The BSG guidelines support this recommendation, noting that PSC-related CCA may be the first manifestation of previously undiagnosed PSC. The EASL-ILCA guidelines strongly recommend abdominal ultrasound surveillance every 6 months for liver fluke-infected populations. Educational campaigns to prevent liver fluke infection are also advocated for as a primary prevention strategy. For patients with choledochal cysts or hepatolithiasis, guidelines suggest individualized surveillance, but specific protocols lack sufficient evidentiary support (*38*).

3.2. Diagnostic methods

3.2.1 Serological diagnosis

All of the guidelines recognize CA 19-9 as the main serum biomarker for CCA diagnosis and prognosis evaluation, but it is non-specific. CEA is an auxiliary marker, and when combined with CA 19-9 it may improve diagnostic accuracy, but none of the guidelines recommend it as a standalone diagnostic tool (*39*).

As technology has advanced, several novel approaches have been developed. Multiple single-center pilot studies have identified miRNAs and circular RNAs in biological fluids (such as serum, plasma, urine, and bile) with diagnostic and/or prognostic potential for CCA (*9,40*). Levels of miR-21 and miR-122 expression in plasma from iCCA patients were significantly higher than those in controls (*41*). Conversely, levels of miRNA-150 expression in patient serum were markedly lower (*42*).

Analysis of mutations in bile cfDNA aids in differentiating benign from malignant biliary strictures when biliary obstruction is suspected (*43*). Moreover, ctDNA plays a crucial role as a prognostic biomarker and monitoring tool for patients with resected eCCA. Patients with persistently negative ctDNA had significantly longer disease-free survival (*44*). Moreover, ctDNA-based genotyping demonstrated acceptable concordance with tissue genomic profiling, establishing liquid biopsy using ctDNA as a valuable adjunct to the genomic analysis of tissue in BTC (*45*).

Emerging translational evidence also strong corroborates the contention that serum extracellular vesicles contain unique protein biomarkers useful for early, sensitive, and specific diagnosis of PSC, CCA, and HCC (*46*). Serum EVs can be used to predict CCA, diagnose it early, and to predict its prognosis. These biomarkers can be detected through whole serum analysis, which is a form of liquid biopsy using tumor cells (*47*).

3.2.2. Diagnostic imaging

All of the guidelines emphasize a multimodal imaging approach for accurate diagnosis and staging. Abdominal ultrasound (US) is the preferred initial imaging method for CCA diagnosis due to its non-invasiveness and accessibility, and it can identify biliary dilatation, intrahepatic masses, and the site of obstruction (*48*). Contrast-enhanced ultrasound (CEUS) can assist in characterizing indeterminate lesions but is not routinely recommended (*49,50*). The ESMO and BSG guidelines recommend contrast-enhanced multiphase CT as an examination for basic staging, evaluating the extent of the primary tumor, determining vascular and lymph node involvement, and identifying metastases. For pCCA and iCCA, MRI/MRCP is preferred to delineate the biliary tree and vascular anatomy. The clinical utility of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) remains a point of slight but notable international divergence. The BSG and NCCN guidelines strongly recommend PET-CT for the highly sensitive detection of occult regional nodal involvement and distant metastatic disease to aggressively prevent futile staging laparotomies and non-curative resections. Conversely, the ESMO guidelines caution against its routine baseline use for primary diagnosis and local hilar staging due to an unacceptably poor specificity (often identifying false-positive inflammatory nodes stemming from cholangitis or stent placement), reserving it primarily for resolving ambiguous distant metastases or confirming the suspected recurrence of disease. Common examinations and their indications are shown in Table 2.

Images contain vast amounts of data and quantitative

Table 2. Summary of diagnostic imaging modalities in cholangiocarcinoma per major guidelines

Diagnostic modality	Primary clinical indication in CCA guidelines	Guideline consensus
Abdominal ultrasound	Serves as the initial screening and triage modality for patients with jaundice; enables the identification of severe biliary dilatation and macroscopic abdominal masses.	Universally recognized as the first-line triage tool for preliminary CCA evaluation.
Multiphasic CT	Applied for anatomical staging of primary cholangiocarcinoma, assessment of macroscopic vascular invasion, and detection of distant metastatic lesions.	Established as the standard diagnostic care recommended by ESMO, EASL, BSG, and NCCN guidelines.
MRI / MRCP	Provides high-precision delineation of biliary tract anatomical structures; evaluates hilar tumor resectability in pCCA.	Accepted as the gold standard for local tumor staging of CCA (ESMO, EASL).
FDG-PET / CT	Facilitates the detection of occult regional lymph node metastasis and unidentified distant metastases in CCA patients.	Recommended for selective clinical application (BSG, NCCN); not preferred for routine local tumor staging (ESMO).
ERCP / Cholangioscopy	Enables direct visual evaluation of biliary lesions and targeted pathological tissue sampling for pCCA and dCCA.	The preferred invasive modality for pathological tissue acquisition in CCA diagnosis.

features that are imperceptible to the human eye. Radiomics plays a pivotal role in analyzing these features, which provide information on tumor shape, size, volume, and other characteristics (*51*). Novel imaging techniques such as AI-assisted diagnostic imaging and multimodal image fusion demonstrate promising efficacy in lesion diagnosis, achieving an accuracy rate (ACC) of 94.7% for distinguishing benign from malignant tumors (*52*). CNN-based computer vision represents the most promising approach for diagnosing extrahepatic CCA through image recognition (*53*). Integrating models with MRI images enables differentiation between high-risk and low-risk CCA groups and lymph node metastasis (*54*). Notably, data quality, scale, and instability significantly impact model research. Recognition algorithms require extensive datasets for validation, which are often difficult to obtain. Concurrently, addressing overfitting and enhancing model robustness and reproducibility remain critical challenges (*55*).

3.2.3. Histological diagnosis

Pathological confirmation is the gold standard for CCA diagnosis, with guidelines emphasizing the importance of tissue sampling for both diagnosis and molecular profiling (*7*):

Biopsy methods: For resectable tumors, the ESMO and BSG guidelines caution against percutaneous biopsy to avoid tumor seeding, suggesting that pathological confirmation can be achieved with surgical specimens (*8,23*). For unresectable or metastatic disease, EUS-guided fine needle aspiration/biopsy (FNA/FNB) is preferred for p/dCCA and GBC, while US/CT-guided biopsy is suitable for iCCA. ERCP/PTC-guided biopsy or cholangioscopy-directed biopsy can be used for biliary strictures, but sensitivity is limited, and combining multiple sampling methods may improve yield.

The 5th WHO classification of biliary tract tumors distinguishes two distinct subtypes of iCCA: the large duct type and the small duct type. The small duct type harbors IDH1/2 mutations and FGFR2 fusions, which are treatable with targeted therapies, while the large duct type often presents with KRAS and SMAD4 mutations similar to pCCA and dCCA (*56,57*).

Immunohistochemistry (IHC): The EASL-ILCA and BSG guidelines recommend IHC panels to distinguish CCA subtypes and exclude metastases: iCCA is typically CK7(+), CK19(+), CK20(-); colon metastases are CK7(-), CK20(+), CDX2(+); lung metastases are TTF-1(+); and breast metastases are GATA3(+). Moreover, iCCA is histologically stratified into small duct (SD) and large duct (LD) subtypes, which exhibit distinct anatomical distributions, growth patterns, and immunophenotypes.

SD-iCCA typically manifests as a mass-forming tumor in the peripheral liver and CD56 and N-cadherin are positive. while LD-iCCA typically affects the perihilar region or extrahepatic bile duct and expresses S100p and mucicarmine (*21,23,58,59*).

Molecular profiling: The ESMO, Canadian, and BSG guidelines strongly recommend next-generation sequencing (NGS) for advanced CCA patients eligible for systemic therapy (*8,20,23*). The core gene panel includes IDH1, FGFR2, HER2, BRAF, and NTRK, with RNA sequencing preferred for detecting FGFR2 and NTRK fusions. Liquid biopsies (cell-free DNA) can be used when tissue is insufficient.

4. Staging and classification

The American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) TNM staging system represents the most widely adopted staging framework for CCA and is recommended by the majority of clinical guidelines (*60*).

For different CCA subtypes, guidelines emphasize subtype-specific staging criteria and clinical assessment considerations. All major guidelines endorse the 8th edition of the UICC TNM staging system, with the following subtype-specific modifications:

For iCCA: Staging is determined by tumor size, multifocality, vascular invasion, lymph node involvement, and distant metastasis. The ESMO and EASL-ILCA guidelines note that the AJCC/UICC system classifies liver metastases without extrahepatic involvement as early-stage disease. However, the European Network for the Study of Cholangiocarcinoma (ENS-CCA) has proposed a new "M1a stage" for multiple liver lesions, as these patients have a poorer prognosis compared to other early-stage patients. Patients with iCCA and liver metastases (approximately 20% of patients) have a significantly worse prognosis than patients with solitary tumors, regardless of lymph node status (*61*).

For pCCA: In addition to TNM staging, the Bismuth-Corlette classification is widely used to characterize the extent of biliary obstruction, which informs surgical planning and biliary drainage strategies.

Type I: Tumor strictly below the primary biliary confluence.

Type II: Tumor involving the primary confluence without extension into secondary ducts.

Type IIIa/IIIb: Tumor extending into the right (IIIa) or left (IIIb) secondary intrahepatic ducts.

Type IV: Bilateral extension into secondary intrahepatic ducts, or multifocal disease precluding standard resection.

All global guidelines stress that the final determination of resectability must not rely on a single clinician's assessment but must be reached through an expert multidisciplinary team (MDT) including hepatobiliary surgeons, medical oncologists, interventional radiologists, endoscopists, and pathologists.

For dCCA: Staging parallels that for pancreatic head carcinoma, with particular emphasis on assessing pancreatic invasion and lymph node metastasis.

In clinical practice, however, staging classifications often diverge from actual patient circumstances, primarily due to inadequate risk stratification. Several alternative staging systems have been proposed to address these limitations. The KKU staging system has been developed specifically for iCCA staging (*62*), and a modified TNM staging system has been used for the long-term OS stratification of iCCA patients (*63*). Additionally, evidence suggests that when tumors directly invade visceral peritoneal surfaces without involving local extrahepatic structures, survival rates do not differ significantly (*64*). Therefore, further refinement of staging systems requires larger-scale, evidence-based validation studies.

5. Treatment

Therapeutic strategies for CCA are categorized into resectable and unresectable cases. The corresponding treatment algorithm is shown in Figure 1. This review focuses on discussing the concept of translational therapy.

5.1. Treatment of resectable CCA

Surgical resection remains the potentially curative treatment modality for CCA, with achieving an R0

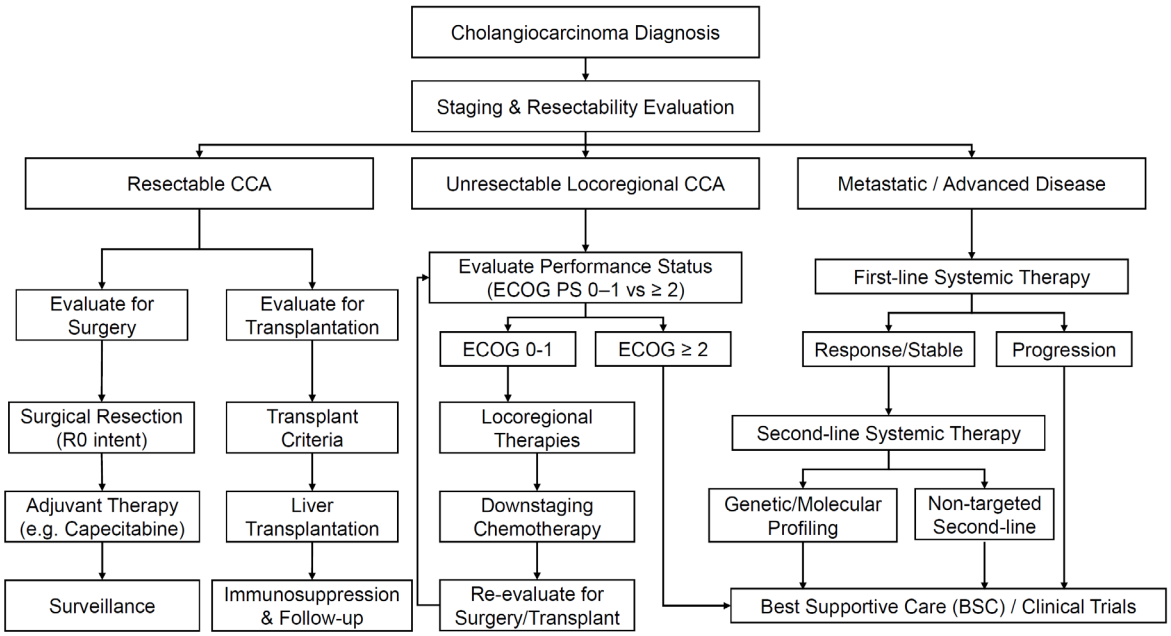

Figure 1. Therapeutic algorithm for cholangiocarcinoma (CCA). This flowchart outlines the corresponding treatment strategies for CCA cases and serves as a visual framework for the subsequent discussion of the concept of therapy in this review.

resection serving as the primary therapeutic objective (*6*). While major clinical guidelines share consistent overarching principles, they differ in certain technical recommendations depending on the CCA subtype.

iCCA: Anatomical hepatectomy—such as hemihepatectomy or segmentectomy—is preferred, accompanied by routine lymphadenectomy with a minimum of six lymph nodes harvested for accurate pathological staging in NCCN. However, large-scale studies at Chinese centers have indicated that while LND is unquestionably critical for accurate N-staging, the procedure itself does not independently improve OS or RFS in patients with clinically node-negative iCCA. Consequently, the primary clinical utility of LND has shifted from a presumed therapeutic clearance to a vital diagnostic tool for risk stratification. The EASL–ILCA guidelines emphasize that anatomical resection is associated with superior survival outcomes compared to non-anatomical resection in patients with stage IB/II iCCA without vascular invasion. Portal vein embolization (PVE) is recommended to augment the future liver remnant (FLR) when the FLR volume is < 25% in patients with normal liver parenchyma or < 40% in those with underlying chronic liver disease (*21*).

For pCCA, extended hepatectomy combined with bile duct resection and caudate lobectomy represents the standard surgical strategy; notably, the BSG guidelines underscore the requirement for preoperative biliary drainage of the FLR, with bilateral drainage indicated in patients presenting with persistent jaundice or cholangitis (*65*). Portal vein or hepatic artery resection and reconstruction may be necessary to achieve R0 margins in advanced Bismuth-Corlette types. In contrast, dCCA is conventionally managed with pancreaticoduodenectomy (Whipple procedure), which routinely includes extended bile duct resection and regional lymphadenectomy.

For GBC, the 2024 IHPBA-APHPBA Delphi Consensus has definitively resolved the long-standing controversy surrounding the surgical management of pT1b GBC, which is defined by tumor invasion of the perimuscular connective tissue without serosal penetration. The optimal extent of hepatic resection for pT1b GBC has frequently been debated in clinical practice. Aggressive surgical strategies have traditionally recommended formal anatomical resection of hepatic segments IVB and V to achieve thorough clearance of deep hepatic parenchymal tissue, whereas alternative approaches have favored a less invasive non-anatomical wedge resection of the gallbladder bed. Notably, the IHPBA-APHPBA Delphi consensus unequivocally recommends margin-negative wedge resection of the gallbladder bed as the sufficient and oncologically radical hepatic procedure for pT1b GBC. In contrast, formal bisegmentectomy of segments IVB/V is strictly reserved for T2 and T3 GBC with confirmed or highly suspected deep hepatic parenchymal invasion (*18*).

Liver transplantation: Liver transplantation is strictly restricted by the ESMO and BSG guidelines to highly selected patients with pCCA arising in the setting of primary sclerosing cholangitis (*8,23*). Eligibility criteria include a tumor size < 3 cm, absence of extrahepatic disease, and completion of neoadjuvant chemoradiotherapy, yielding 5-year survival rates ranging from 55 to 82%. For iCCA, the ILTS-ILCA 2024 and ENS-CCA 2026 guidelines suggest that transplantation be considered only for early-stage tumors (< 3 cm) in patients with underlying cirrhosis (*9,17*). Although current evidence supporting liver transplantation as a therapeutic modality for CCA remains limited by the lack of large-scale, prospective, multicenter studies, it represents an important treatment option for selected patient populations (*66*).

Adjuvant therapy: All of the major clinical guidelines endorse six months of oral capecitabine as standard adjuvant therapy based on the landmark BILCAP trial, which noted a significant OS benefit. The Japanese ASCOT trial further supports the efficacy of S-1 as an alternative adjuvant regimen, particularly in Asian populations. Additionally, the ESMO and BSG guidelines suggest considering adjuvant chemoradiotherapy for R1-resected GBC or p/dCCA, although the supporting evidence remains limited.

Large-scale retrospective evidence further substantiates the role of adjuvant therapy in resectable CCA. In 4,519 patients with CCA who underwent surgical resection, adjuvant therapy was associated with favorable outcomes in low-risk resectable disease, defined as patients with R0 resection margins and negative regional lymph nodes (hazard ratio (HR): 0.86, 95% confidence interval (CI): 0.78–0.95) (*67*). Similarly, for high-risk individuals who underwent surgical resection between 2010 and 2018, the implementation of adjuvant chemotherapy (AC) contributed to improved clinical outcomes (*68*).

5.2. Treatment of unresectable CCA

The stark reality of CCA is that the majority of patients present with locally advanced, unresectable, or metastatic disease. In this setting, management focuses on prolonging survival, maintaining quality of life, and aggressively alleviating symptoms such as biliary obstruction and cancer-related pain.

5.2.1. First-line therapy

As first-line therapy for advanced CCA, gemcitabine plus cisplatin (GemCis) has long been the standard systemic regimen. The phase III TOPAZ-1 trial demonstrated that the addition of durvalumab, a PD-L1 inhibitor, to GemCis significantly improves overall survival, leading the ESMO, Canadian, and BSG guidelines to endorse GemCis combined with durvalumab as the preferred first-line treatment. Similarly, the KEYNOTE-966 trial reported a survival benefit with pembrolizumab plus

GemCis, although this regimen is currently approved only in select regions. In Asian populations, particularly per the CSCO guidelines, the combination of gemcitabine with S-1 is considered non-inferior to GemCis, offering an alternative backbone with a favorable toxicity profile. For patients with a poor performance status (ECOG PS = 2), gemcitabine monotherapy is recommended as a less toxic alternative. In cases of renal impairment, oxaliplatin may be substituted for cisplatin to avoid nephrotoxicity while maintaining therapeutic efficacy (*8,20,23,69*).

5.2.2. Second-line therapy

In the second-line and subsequent treatment of advanced CCA, FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) is established as the standard regimen based on the ABC-06 trial, which noted that it had a significant overall survival benefit. Liposomal irinotecan combined with 5-FU/leucovorin represents an alternative option, although its efficacy varies between Western and Asian populations (*16*).

For molecularly selected patients, targeted therapies play a critical role: FGFR2 fusions can be treated with FDA- and EMA-approved inhibitors—pemigatinib, infigratinib, and futibatinib—yielding a median PFS of 6.9–9.0 months, and they are recommended by the ESMO and Canadian guidelines after first-line progression (*14*). Ivosidenib, an IDH1 inhibitor, significantly improves PFS in IDH1-mutant BTC and is FDA-approved, though it lacks EMA approval and Canadian reimbursement. For tumors harboring BRAF V600E mutations, combination therapy with dabrafenib and trametinib demonstrates robust activity (objective response rate (ORR): 51%; median OS: 14 months) and is endorsed for eligible patients. NTRK gene fusions, although exceedingly rare (< 0.1% of BTC), are targetable with the tumor-agnostic TRK inhibitors larotrectinib or entrectinib. Similarly, RET inhibitors have also shown efficacy in some patients. In HER2-amplified BTC, dual HER2 blockade with pertuzumab plus trastuzumab or antibody–drug conjugates such as trastuzumab deruxtecan show modest efficacy (ORR: 23–36%) and are generally offered within clinical trials or special access programs. Finally, pembrolizumab is recommended for the subset of patients with high microsatellite instability (MSI-H) or mismatch repair–deficient (dMMR) CCA, based on KEYNOTE-158 data indicating an ORR of 40.9% and a median OS of 24.3 months. (Table 3)

5.2.3. Locoregional therapy

Locoregional treatments (LRT) are critical for palliation, symptom control, and prolonging survival, particularly in liver-predominant unresectable disease or cases presenting with profound obstructive jaundice. Biliary drainage is of the utmost importance so that malignant biliary obstruction is promptly relieved in order to prevent ascending cholangitis, alleviate pruritus, and reverse hyperbilirubinemia, thus enabling the safe administration of systemic chemotherapy. For dCCA, the EASL and BSG guidelines prefer endoscopic biliary drainage (EBD) *via* ERCP over percutaneous transhepatic biliary drainage (PTBD) due to lower risks of hemorrhage and external tube dislocation. Endoscopic drainage is technically arduous in pCCA (Bismuth III/IV). The current EASL and BSG consensus indicates parity between ERCP and PTBD; the choice depends strictly on local MDT expertise and anatomical feasibility.

In addition to biliary drainage, local treatment of the tumor tissue is also imperative. According to the ESMO and EASL–ILCA guidelines, thermal ablation is recommended for patients with unresectable iCCA lesions ≤3 cm, demonstrating a pooled complete ablation rate of 93% and a median OS of 30.2 months. For liver-confined disease, transarterial approaches—including transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and hepatic arterial infusion chemotherapy (HAIC)—represent feasible therapeutic options that may enhance ORRs and facilitate secondary resection, particularly when integrated with systemic therapy. Notably, transarterial therapeutic approaches may demonstrate optimal efficacy in larger lesions (>4 cm) with peripheral enhancement, potentially reflecting increased dependence on arterial blood supply, thereby

Table 3. Actionable molecular targets in cholangiocarcinoma: Prevalence, targeted agents, and corroborating guideline

Molecular target	Prevalence	Targeted agent(s)	Corroborating guideline (NCCN / ESMO)
FGFR2 fusions	10-15% (iCCA)	Pemigatinib, Futibatinib, Erdafitinib	Category 2A / ESCAT I-B
IDH1 mutations	15-20% (iCCA)	Ivosidenib	Category 1 / ESCAT I-A
HER2 amplification	5-15% (GBC, eCCA)	Trastuzumab deruxtecan, Zanidatamab, Trastuzumab + Pertuzumab	Category 2A / ESCAT I-C
BRAF V600E	3-5% (iCCA)	Dabrafenib + Trametinib	Category 2A / ESCAT I-B
MSI-H / dMMR	1-2% (all subtypes)	Pembrolizumab,	Category 2A / ESCAT I-C
		Dostarlimab	Category 2B / ESCAT I-C
NTRK fusions	<1% (all subtypes)	Larotrectinib, Entrectinib, Repotrectinib	Category 2A / ESCAT I-C
RET fusions	<1% (all subtypes)	Pralsetinib	Category 2B / ESCAT I-C
		Selpercatinib	Category 2A / ESCAT I-C
None (wild-type)	~60% (all subtypes)	mFOLFOX or Nal-IRI + 5-FU	Category 1 (FOLFOX)

augmenting treatment effectiveness (*70*).

Stereotactic body radiotherapy (SBRT) provides effective palliative control for locally advanced iCCA, with a reported 1-year local control rate of 83%. However, SBRT is not recommended as a definitive treatment modality outside the context of clinical trials. The optimal management strategy for patients with locally advanced CCA involves a rational combination of multiple locoregional therapeutic approaches, complemented by continually evolving systemic treatment regimens. In the absence of Level 1 evidence to guide clinical decision-making, all patients with CCA should undergo comprehensive evaluation at experienced centers with multidisciplinary expertise (*71*).

5.2.4. Translational therapy

Translational therapy represents a treatment paradigm that integrates systemic and local therapeutic modalities to render initially unresectable advanced carcinoma amenable to curative surgical intervention (*72*). The core mechanism entails combining targeted therapy and immunotherapy with local interventions, including TACE and HAIC. This multimodal approach induces tumor regression, thereby facilitating tumor downstaging.

Multi-agent regimens (*e.g.*, GemCis + immunotherapy) can achieve substantial tumor shrinkage, allowing successful R0 resections in iCCA or pCCA that was previously deemed inoperable. Immunotherapy has emerged as a promising therapeutic strategy across various malignancies in clinical oncology. The fundamental principle of tumor immunotherapy involves modulating the tumor microenvironment (TME) and restoring immune surveillance of tumor cells to achieve antitumor action. Notably, specific patient subpopulations derive substantial benefits from targeted immunotherapeutic interventions, underscoring the increasing importance of precision medicine in identifying eligible candidates for CCA management. Among the classic diagnostic methodologies, including immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR)-based assays, the latter demonstrates superior efficiency in detecting single-gene mutations (*73*).

CCA is characterized by a prominent stromal component comprising heterogeneous cell populations, including both innate and adaptive immune cells. Tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and cancer-associated fibroblasts (CAFs) collectively shape the immune microenvironment of CCA (*74*). Elevated expression of immune checkpoint molecules, including programmed cell death protein 1 (PD-1), its ligand PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), on tumor-infiltrating immune cells reflects an immunosuppressive milieu (*75*). Consequently, the tumor-infiltrating immune environment (TIME) promotes tumor progression, immune evasion, and chemoresistance, contributing to the limited efficacy of immune checkpoint inhibitor (ICI) therapy observed in clinical trials (*76*).

Current clinical guidelines provide specific recommendations for ICI therapy in CCA. The 2025 NCCN guidelines endorse pembrolizumab, an anti-PD-1 ICI, as monotherapy for unresectable or metastatic CCA exhibiting MSI-H or dMMR. This recommendation is consistent with the 2022 ESMO guidelines for biliary tract cancers (*10,14,77*). Moreover, ESMO recommends NGS for comprehensive molecular profiling in CCA (*78*). Recurrent genomic alterations in advanced CCA include FGFR2 fusions (*79*), ERBB2 (HER2) amplifications (*80*) and mutations (*81*), and BRAF mutations (*82*). Although FGFR inhibitors demonstrate clinical benefit in CCA harboring FGFR2 fusions or rearrangements, therapeutic outcomes remain suboptimal. Their clinical utility is further constrained by dose-dependent toxicities and the inevitable emergence of acquired resistance (*79,83*). Similarly, despite limitations including small cohort sizes and the absence of control groups, mounting evidence suggests that HER2-targeted therapy holds promise for patients with CCA (*84*).

IDH1 mutations represent a rare metabolic enzyme alteration in CCA. While emerging data indicate potential OS benefits, the current understanding of resistance mechanisms remains limited (*85*). Notably, the Japanese guidelines do not currently provide recommendations for patients with genomic alterations in the FGFR or IDH genes (*86*).

In summary, although treatment options beyond standard chemotherapy may be available for patients with CCA, additional prospective data need to be gathered to establish the efficacy of incorporating targeted therapies in various treatment stages or combining them with chemotherapy and other therapeutic modalities (*87*).

6. Discussion

CCA remains a highly aggressive and molecularly heterogeneous malignancy with a persistently poor prognosis. The management of CCA is complex, necessitating a synthesis of the global consensus on stratified care while accounting for significant regional disparities driven by local etiologies and resource availability.

Regional disparities significantly influence the management of CCA, with clinical guidelines tailored to local etiologies and resource availability. In Asia, screening and treatment strategies prioritize liver fluke infection and hepatolithiasis-related CCA, and the oral fluoropyrimidine S-1 is commonly used in both adjuvant and palliative settings. The "Lawa model" program in Thailand, combining anthelmintic treatment, intensive health education, ecosystem monitoring, and community participation, reduced infection rates in cyprinoid fish

(the intermediate host) from 70% to less than 1% (*88,89*). Conversely, Europe and North America focus on PSC-associated CCA, benefiting from broader access to immunotherapies (*e.g.*, durvalumab) and targeted agents such as FGFR inhibitors. In resource-limited regions, cost constraints necessitate reliance on US-based surveillance and gemcitabine-based chemotherapy, while NGS and molecularly targeted therapies remain largely inaccessible. These geographic variations underscore the need for context-specific guideline development and equitable access to advanced therapeutics (*90,91*).

Despite these geographic differences, the core principle of optimizing outcomes relies on stratified management based on resectability status. First, patients with initially resectable CCA undergo upfront curative-intent resection, the only established radical therapy, in 20–30% of newly diagnosed cases. Adjuvant capecitabine for 6 months is universally recommended following R0 resection and is corroborated by evidence from the phase III BILCAP trial (*92*). Second, patients with borderline resectable CCA receive neoadjuvant systemic therapy to facilitate downstaging, followed by resection and adjuvant treatment, in order to improve margin-negative resection rates and reduce recurrence (*9,15*).

Third, patients with initially unresectable CCA responding to treatment receive first-line therapy combining cisplatin, gemcitabine, and anti–PD-1/PD-L1 inhibitors (TOPAZ-1, KEYNOTE-966); eligible patients then undergo salvage resection or liver transplantation, a validated curative approach for selected intrahepatic and perihilar CCA (*93,94*). Fourth, patients with persistently unresectable/metastatic C receive palliative systemic therapy to prolong survival[1]. Second-line FOLFOX is standard for patients without actionable alterations (ABC-06), whereas matched targeted agents are used for IDH1 mutations (ClarIDHy), FGFR2 fusions, BRAF V600E, or HER2 amplification (*95-97*).

Emerging research underscores the importance of molecular subtyping in guiding therapeutic decision-making. According to the EASL-ILCA recommendations, SD-iCCA frequently harbors IDH1/2 mutations and FGFR2 fusions, whereas LD-iCCA and eCCA have abundant KRAS and SMAD4 alterations (*21*). These molecular distinctions may inform subtype-specific treatment strategies and patient stratification. Despite therapeutic advances over the past decade, improvements in survival rates for advanced CCA remain limited. This observation highlights the critical need for identifying specific biomarkers to improve patient prognosis and therapeutic efficacy. Priority must be given to preventive measures, early diagnosis, and the identification of predictive biomarkers to achieve optimal patient stratification (*98,99*).

Drug resistance remains a major challenge in CCA management (*100*). Resistance to FGFR and IDH1 inhibitors arises through secondary gatekeeper mutations or activation of bypass pathways, prompting investigation into irreversible FGFR inhibitors and rational combinations with immunotherapy (*101*). Similarly, the limited efficacy of immune checkpoint inhibitors—attributed to a low tumor mutational burden and an immunosuppressive microenvironment—is being addressed through multimodal approaches, including chemotherapy, anti-VEGF agents, and personalized vaccines. Chemoresistance mechanisms involving DNA repair dysregulation and drug efflux pumps are actively being studied, with PARP inhibitors showing potential in BRCA1/2-mutated subsets. These findings suggest that combination strategies targeting multiple pathways simultaneously may overcome resistance mechanisms more effectively than monotherapy.

For refractory disease, a precision oncology approach is advocated, including repeat molecular profiling *via* tissue re-biopsy or liquid biopsy to uncover acquired actionable alterations (*102,103*), prioritized enrollment in clinical trials evaluating emerging agents (*e.g.*, Claudin 18.2 or MET inhibitors), and integration of locoregional therapies for oligoprogressive disease. Appropriate patient selection, resection with negative surgical margins, and rational administration of systemic chemotherapy remain critical factors for ensuring optimal long-term survival outcomes (*104*).

Critical gaps persist in prevention and early detection (*21*). Prospective data validating the cost-effectiveness of screening high-risk cohorts remain lacking, and novel non-invasive biomarkers, such as circulating tumor DNA and microRNAs, require further validation. Moreover, the long-term impact of public health interventions—particularly educational campaigns in liver fluke-endemic areas—on the incidence of CCA has yet to be quantified. These limitations highlight the need for large-scale, prospective, multicenter studies to establish evidence-based screening protocols.

The integration of spatial transcriptomics with radiomics, encompassing comprehensive analysis of bulk, single-cell, and spatial transcriptomics, holds promise for predicting prognosis and immunotherapeutic benefits, thereby facilitating precision oncology in treatment decision-making for iCCA patients (*105*). This emerging technology may enable more accurate patient stratification and treatment personalization in future clinical practice.

Concurrently, early palliative care involvement is essential to managing complications such as biliary obstruction, pain, and malnutrition, thereby optimizing quality of life, and particularly in patients with a poor performance status for whom best supportive care may be most appropriate. This multidisciplinary approach should be integrated throughout the disease continuum rather than reserved for end-stage disease.

7. Conclusion

Current CCA guidelines share core principles

in epidemiology, diagnosis, and treatment but differ in regional adaptations and resource-based recommendations. The integration of recent key studies has enriched the treatment landscape, with immunotherapy combined with chemotherapy becoming the new first-line standard, and targeted therapies providing personalized options for molecularly defined subgroups. However, several issues remain unaddressed, including drug resistance, lack of universal screening standards, and limited access to advanced therapies in resource-limited regions. Future research should focus on clarifying molecular mechanisms, developing novel biomarkers, optimizing combination therapies, and validating prevention strategies to improve the prognosis for CCA patients.

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